STATISTICAL ANALYSIS PLAN

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Principle Investigator:	PPD , MD, MPH
Sponsor:	Capricor Therapeutics 8840 Wilshire Blvd, 2nd Floor Beverly Hills, CA 90211

CONFIDENTIALITY STATEMENT


PPD

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TABLE OF CONTENTS

APPROVALS **3**
REVISION HISTORY **4**
LIST OF ABBREVIATIONS **7**
PREFACE **9**
1. INTRODUCTION **10**
2. STUDY OBJECTIVES, TREATMENTS, AND ENDPOINTS **10**
2.1 Objectives 10
2.2 Treatment Group Comparisons 10
2.3 Study Assessments 10
2.3.1 Safety Assessments 10
2.3.2 Exploratory Efficacy Endpoints 12
3. STUDY DESIGN AND SCHEDULE OF EVENTS **13**
4. SAMPLE SIZE **14**
5. RANDOMIZATION **14**
6. ANALYSIS POPULATIONS **14**
7. DATA MANAGEMENT, PRESENTATION, AND ANALYSIS CONSIDERATIONS **15**
7.1 Programming Environment 15
7.2 Tables, Figures, and Listings 15
7.2.1 Tables and Figures 15
7.2.2 Listings 15
7.3 Data Analysis 15
7.4 Subgroups 16
7.5 Missing Data 16
7.6 Study Period and Time Point Definitions 17
7.7 Visit Windows 17
8. STUDY POPULATION PARAMETERS **18**
8.1 Analysis Populations 18
8.2 Eligibility and Informed Consent 18
8.3 Baseline Characteristics 19
8.4 Medical History 19
8.5 Serology and Coagulation 19

8.6 IP Administration 19
8.7 Subject Study Progress 19
8.8 Subject Disposition 19
9. SAFETY ANALYSIS 20
9.1 Adjudicated Clinical Events 20
9.2 Adverse Events 20
9.3 Concomitant Medications 21
9.4 Safety Laboratory Evaluations 21
9.5 Vital Signs, Height, Weight, and BMI 22
9.6 Physical Examination 23
9.7 12-Lead ECG and Continuous Cardiac Monitoring 23
10. EXPLORATORY EFFICACY ANALYSIS 23
10.1 MRI Parameters 24
10.2 Mobility Parameters 26
10.2.1 PUL Scale 26
10.2.2 Spirometry 26
10.2.3 6MWT 26
10.3 QoL 26
10.3.1 PedsQL – DMD Module 26
10.3.2 Pediatric Outcomes Data Collection Instrument (PODCI) 27
11. OTHER DATA COLLECTED 29
11.1 Missed Visits and Assessments 29
11.2 Protocol Violations/Deviations 29
12. CLINICAL EVENTS COMMITTEE 30
13. SEQUENCE OF PLANNED ANALYSES 31
13.1 Interim Safety Reviews 31
13.2 Administrative Interim Analyses 31
13.2.1 Pre-Month 6 31
13.2.2 Month 6 31
13.3 Final Analysis 31
14. DSMB 32
15. DEVIATIONS FROM STATISTICAL METHODS IN THE PROTOCOL 32
REFERENCES 33
APPENDIX A: SCHEDULE OF EVENTS 34
APPENDIX B: TABLES OF CONTENTS FOR TABLES, FIGURES, AND LISTINGS 36

LIST OF ABBREVIATIONS

ABBREVIATION	DEFINITION
6MWT	Six-Minute Walk Test
AE	adverse event
BMI	body mass index
CEC	Clinical Events Committee
CI	confidence interval
CK-MB	creatine phosphokinase MB isoenzyme
CSR	Clinical Study Report
DMD	Duchenne muscular dystropy
DSMB	Data Safety Monitoring Board
DSA	donor specific antibodies
ECG	electrocardiogram
ELISPOT	enzyme-linked immunosorbent spot
EOS	end of study
FBS	fetal bovine serum
$FEF_{25-75\%}$	forced expiratory flow at 25-75% of FVC
FET	forced expiratory time
FEV_1	forced expiratory volume in 1 second
FVC	forced vital capacity
HbA1c	glycosylated hemoglobin
HBsAg	hepatitis B surface antigen
HCV	hepatitis C virus
HIV	human immunodeficiency virus
HLA	human leukocyte antigen
ICH	International Conference on Harmonisation
IL-10	Interleukin 10
IP	investigational product
ITT	intent-to-treat
LGE	late gadolinium enhancement
LS	least-squares
LTFUP	Long-Term Follow-up
LV	left ventricular
LVEDV	LV end diastolic volume
LVEF	left ventricular ejection fraction
LVESV	LV end systolic volume
M	million
MACE	major adverse cardiac event
MAR	missing at random

MedDRA	Medical Dictionary for Regulatory Activities
MFI	mean fluorescence intensity
MI	myocardial infarction
mITT	modified intent-to-treat
ML	maximum likelihood
MNAR	missing not at random
MRA	mineralocorticoid receptor antagonist
MRI	magnetic resonance imaging
PedsQL	Pediatric Quality of Life
PEF	peak expiratory flow
PHA	phytohemagglutinin
PODCI	Pediatric Outcomes Data Collection Instrument
PT	Preferred Term
PUL	Performance of Upper Limb
QoL	quality of life
SAE	serious adverse event
SAP	Statistical Analysis Plan
SD	standard deviation
SDF1	stromal cell derived factor 1
SOC	System Organ Class
TEAE	treatment-emergent adverse event
TFLs	tables, figures, and listings
TMPG	TIMI myocardial perfusion grade
VT	ventricular tachycardia
WHO-DD	World Health Organization Drug Dictionary

PREFACE

The purpose of this statistical analysis plan (SAP) is to describe the planned statistical analyses and reporting for Capricor Protocol CAP-1002-DMD-01 (HOPE). The planned analyses identified in this SAP may be included in future manuscripts. Exploratory analyses not necessarily identified in this SAP may be performed to support planned analyses. Any post-hoc or unplanned analyses not specified in this SAP will be clearly identified as such in the Clinical Study Report (CSR) and manuscripts for publication.

The SAP is a supplement to the study protocol, which should be referred to for additional details on study design, study conduct, and other operational aspects of the study.

The structure and content of the SAP provides sufficient detail to meet the requirements identified by the Food and Drug Administration and International Conference on Harmonisation (ICH) E9: Guidance on Statistical Principles in Clinical Trials.[1] All work planned and described in the SAP will follow internationally accepted guidelines published by the American Statistical Association. The following documents were also considered in preparation for writing this SAP:

- Clinical Research Protocol CAP-1002-DMD-01, Amendment 3.0, July 18, 2016
- ICH E3 Guideline: Structure and Content of Clinical Study Reports[2]
- ICH E6 Guideline on Good Clinical Practice[3]
- ICH E8 General Considerations for Clinical Trials[4]

1. INTRODUCTION

Duchenne muscular dystrophy (DMD) is a pediatric-onset, genetic disease in which patients lack dystrophin, a protein critical for stabilizing muscle cell membranes. Affecting 1 in 3,500-5,500 male births, DMD accounts for 80% of all cases of muscular dystrophy. Patients experience progressive skeletal muscle weakness and loss of ambulation by age 15, eventual respiratory and cardiac failure, and an abbreviated lifespan. With the use of corticostertoids and noninvasive ventilation to treat respiratory muscle disease, heart failure has emerged as the main cause of death in DMD patients. Approved therapies for the underlying disease currently are limited to eteplirsen, an exon 51 skipping agent in dystrophin pre-mRNA to enable the synthesis of a shortened and functional form of dystrophin protein. Allogeneic cardiosphere-derived cells (CAP-1002) are an investigational product consisting of allogeneic cardiosphere-derived cells, known to secrete numerous bioactive elements upon delivery, which is thought to lead to global cardiovascular benefits. The HOPE-Duchenne Phase 2 trial will be the first investigation of CAP-1002 in male subjects with cardiomyopathy secondary to DMD and the first trial of the product not conducted exclusively in adults. The delivery approach will be multivessel intracoronary infusion to distribute the cells throughout the myocardium.

2. STUDY OBJECTIVES, TREATMENTS, AND ENDPOINTS

2.1 Objectives

The primary objective of HOPE is to evaluate the safety and tolerability of CAP-1002 administered by multi-vessel intracoronary infusion in subjects with cardiomyopathy secondary to DMD.

The secondary objective of HOPE is to explore the efficacy of CAP-1002 administered by multi-vessel intracoronary infusion in subjects with cardiomyopathy secondary to DMD.

2.2 Treatment Group Comparisons

Two treatment groups will be compared in the study:

- CAP-1002 (single administration of 75 million (M) cells split into a triple vessel infusion of 25 M cells each)
- Usual Care

2.3 Study Assessments

2.3.1 Safety Assessments

Safety will be assessed at 6 and 12 months post infusion or reference date unless otherwise noted. For usual care subjects, the reference time point will be randomization date + 7 days at 9:00 a.m. (subject's local time).

1) Adjudicated clinical events:
   a) The following events occurring during or post infusion or reference time point:

- For subjects who receive CAP-1002 only, new TIMI flow 0-2 or TIMI myocardial perfusion grade (TMPG) 0-2, noted immediately following intracoronary infusion of investigational product (IP) and persisting > 3 min after IP infusion, despite intracoronary vasodilator administration.

- Within 72 hours of intracoronary infusion or reference time point, sudden unexpected death defined as occurring within 1 hour of symptom onset, or unwitnessed death in a person previously observed to be well within the preceding 24 hours without an identified caused.

- Major adverse cardiac events (MACE) within 72 hours of intracoronary infusion or reference time point, including death, non-fatal myocardial infarction and hospitalization for cardiovascular event (including heart failure hospitalizations). Evidence of myocardial injury will be assessed by a rule out myocardial infarction (MI) cardiac enzyme protocol following IP administration. Among subjects who receive CAP-1002, troponin and creatine phosphokinase MB isoenzyme (CK-MB) will be obtained every 8 hours for 20-24 hours after IP infusion.

b) Sudden unexpected death defined as occurring within one hour of symptom onset, or unwitnessed death in a person previously observed to be well within the preceding 24 hours without an identified cause.

c) MACE, including death, non-fatal myocardial infarction, hospitalization for cardiovascular event (including heart failure hospitalizations), emergency room treatment for heart failure, left ventricular assist device or heart transplant.

d) Any hospitalization due to a cardiovascular cause.

e) Any inter-current cardiovascular illness which prolongs hospitalization.

f) Development of, or an increase in the frequency of, ventricular tachycardia (VT) with duration of 30 seconds or longer ascertained by protocol mandated continuous cardiac monitoring via Holter Monitor or ZIO® Patch.

g) Development of increased anti human leukocyte antigen (HLA) antibody levels with development of sensitization to HLA antigens specific to the CAP-1002 CDC donor. Elevation of donor-specific antibodies (DSA) is defined as mean fluorescence intensity (MFI) above a threshold of 5000; a threshold of 1000 MFI will also be used to evaluate elevation of DSA. See Section 9.1 for details related to comparison between CAP-1002 and usual care subjects.

2) Adverse events (AEs)
3) Concomitant medications
4) Change from baseline in laboratory evaluations
5) Peak elevation in troponin and CK-MB levels following IP infusion or on reference date

6) Changes from baseline in vital signs, weight, and body mass index (BMI)
7) Changes from baseline on general and cardiac physical examinations
8) Changes from baseline in electrocardiogram (ECG), both 12-lead ECG and continuous cardiac monitoring

2.3.2 Exploratory Efficacy Endpoints

The following exploratory efficacy endpoints will be assessed at 6 and 12 months post infusion or reference date:

1) Change from baseline in cardiac structural parameters measured by magnetic resonance imaging (MRI), including:
   - LV late gadolinium enhancement (LGE) expressed as a percent of LV mass
   - LV LGE expressed in grams
   - LV viable mass expressed in grams
   - Number of LV segments with LGE
   - LV circumferential strain
   - Left ventricular ejection fraction (LVEF)
   - LV end diastolic volume (LVEDV) and LV end systolic volume (LVESV)
   - LV stroke volume
   - Regional LV function assessment

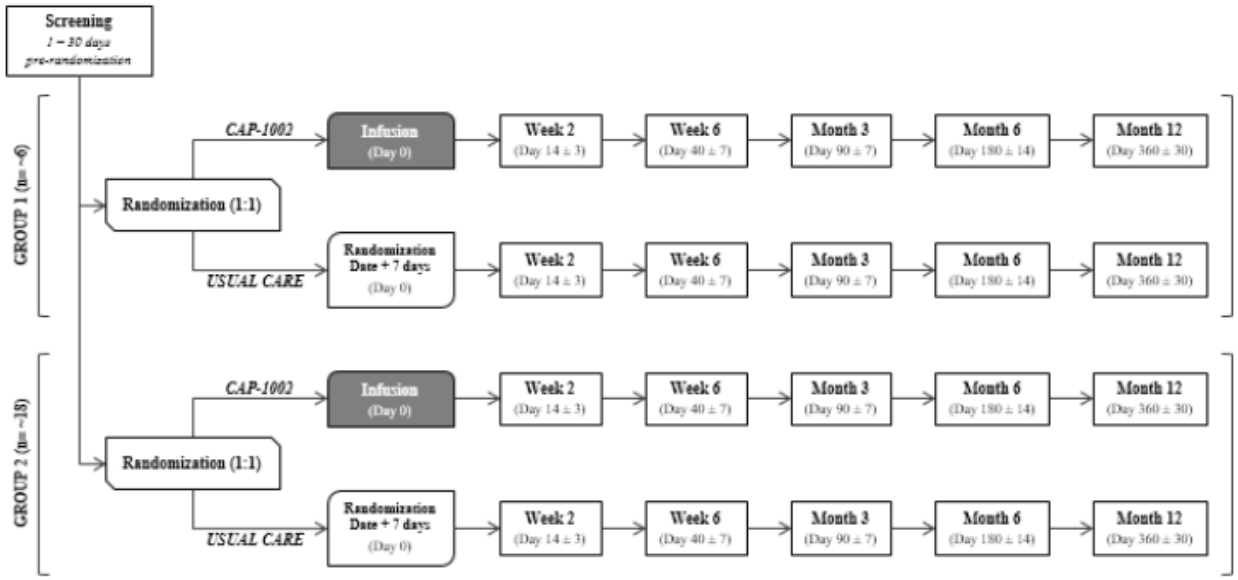
   LGE and circumferential strain will be assessed both overall as well as by individual segment and by groups of segments (e.g., infusion location, septum, base, LV free wall).
2) Rate of change since baseline compared to rate of change from historical MRI to baseline in LV LGE (overall and by individual segment and groups of segments)
   - expressed as a percent of LV mass
   - expressed in grams
3) Change from baseline in functional parameters:
   - Performance of Upper Limb (PUL) scale
   - Spirometry
   - 6-minute walk test (6MWT) in ambulatory patients
4) Change from baseline quality of life (QoL) parameters:
   - Pediatric Quality of Life Inventory (PedsQL), including the cardiac module
   - Pediatric Outcomes Data Collection Instrument (PODCI) Adolescent Questionnaire
5) Change from baseline in biomarkers:
   - Osteopontin
   - ST2
   - Interleukin 10 (IL-10)
   - Galectin-3

3. STUDY DESIGN AND SCHEDULE OF EVENTS

This is a randomized, open-label, controlled phase 2 trial designed to evaluate the safety and tolerability and explore the efficacy of CAP-1002 administered by multi-vessel intracoronary infusion in subjects with cardiomyopathy secondary to DMD. Approximately 24, and not more than 30, subjects will be randomized 1:1 to receive CAP-1002 or usual care. Subjects randomized to receive usual care will continue to be cared for and treated on an ongoing basis in whatever manner the investigator deems most appropriate for the subject. The first 6 subjects enrolled (Group 1) will be older than 18 years of age. Enrollment of the remaining subjects (Group 2) will begin at least two weeks after the final infusion occurs in Group 1 to allow a review of Group 1 safety data through 72 hours post infusion. Subjects in Group 2 will be at least 12 years of age.

CCI [redacted] Anatomically one of the three coronary arteries infused must supply more than 30% of the LV myocardium. CCI [redacted]

Subjects will undergo protocol assessments through 12 months post infusion or reference date. Reviews by a Data Safety Monitoring Board (DSMB) will be done after Group 1 completes 72 hours of follow-up and throughout the trial per charter but at least semi-annually. The DSMB will review both safety and efficacy data after all subjects complete 6 months of follow-up or withdraw from the study. In addition, there will be one administrative interim efficacy analysis after Month 6 MRI measurements are available for at least 14 subjects. Subjects will be followed annually for 5 years post infusion or reference date. The Schedule of Events is shown in Appendix A. A schematic of the study design is as follows:



4. SAMPLE SIZE

The sample size of approximately 12 subjects per treatment group is adequate to assess safety and tolerability and to explore efficacy.

5. RANDOMIZATION

Randomization will be done by a dominant biased coin design[5] within each of 5 blocks of 6 subjects each. This design allows decreasing predictability as more subjects become enrolled. For a given block, let $D_N = n_c - n_u$, where n_c = number randomized to CAP-1002 and n_u = number randomized to usual care, and N = total randomized to date, N=0 to 5. For block = B, B=1 to 5, let p_{N+1} = probability the next assignment will be CAP-1002. Then p_{N+1} varies according to the following rules:

$p_{N+1} = 0.5$ if $D_N = 0$
$p_{N+1} = p_B$ if $D_N > 0$
$p_{N+1} = 1\text{-}p_B$ if $D_N < 0$

The specific values of p_B (for each block) will be known only to the study statistician until after database lock.

6. ANALYSIS POPULATIONS

The following analysis populations are defined for the trial:

Safety Population: Subjects randomized to CAP-1002 treatment who received the IP on Day 0, and all subjects in the usual care treatment group who remain on study as of the reference time point. Subjects will be summarized and analyzed per treatment actually received, regardless of their randomization assignment.

Intent to Treat (ITT) Population: All subjects randomized. Subjects will be summarized and analyzed per their randomization assignment, regardless of the treatment (CAP-1002 or usual care) actually received.

Modified ITT (mITT) Population for Efficacy Parameter X: Subjects in the safety population who have at least one post-baseline observation for Parameter X. Subjects will be summarized and analyzed per their randomization assignment, regardless of the treatment actually received.

Per Protocol Population: Subjects with no major protocol violations. The list of subjects with major protocol violations will be compiled prior to database lock.

7. DATA MANAGEMENT, PRESENTATION, AND ANALYSIS CONSIDERATIONS

7.1 Programming Environment

SAS® version 9.4 or higher (SAS Institute, Cary, North Carolina) will be used for statistical analyses and the production of tables, figures, and listings (TFLs).

7.2 Tables, Figures, and Listings

Tables of contents for TFLs to be produced are shown in Appendix B. All TFLs will be appended to the final CSR.

7.2.1 Tables and Figures

- Tables and figures will present data summaries and/or analyses for the appropriate study population; e.g., summaries of safety parameters will be shown for the safety population only.
- Treatment group order in tables and figures will be usual care, CAP-1002, and "All Subjects." Note: not all tables and figures will show data summarized for "All Subjects."
- Tables and figures will present summaries/analyses by study visit window, if applicable.
- Table column headers and figure legends will include subgroup sample sizes.

7.2.2 Listings

- Listings will present all data collected for all subjects unless the listing applies only to a specific analysis population (e.g., a listing of treatment-emergent AEs applies only to the safety population).
- Listings will be ordered by unique subject identifier, study visit window (see Section 7.7), date, and data collection time.

7.3 Data Analysis

- The anchor date used for summaries and analyses will depend on the analysis population, as follows:
  - ITT population: randomization date
  - mITT population: IP administration or reference date

  - Safety population: IP administration or reference date
  - Per protocol population: IP administration or reference date

- Categorical variables will be summarized as frequencies and percentages in each category. Percentages will be reported to one decimal place. Unless otherwise noted in Sections 8-10, categorical variables will be analyzed using chi square tests of association or, if any contingency table cell has less than 5 subjects, Fisher's exact test.
- Continuous variables will be summarized by numbers of subjects, means, standard deviations, medians, and ranges. The number of decimal places for minimums and maximums will be the same as the original data. The number of decimal places for means, medians, and interquartile ranges will be the same as the original data plus one. The number of decimal places for measures of variance will be the same as the original data plus two. Unless otherwise noted in Sections 8-10, continuous variables will be analyzed using t-tests or, if appropriate, analysis of covariance with baseline as a covariate. Non-parametric tests and data transformations will be considered for variables with distributions that violate parametric assumptions.
- Data with qualifiers (e.g., "<") will be listed with but summarized without the qualifier.
- P-values will be presented to two decimal places if > 0.01, to three places if < 0.01 but > 0.001, and to four places if < 0.001 but > 0.0001. P-values < 0.0001 will be presented as "< 0.0001."
- Statistical tests will be two-sided and tested at the 0.05 significance level unless otherwise noted in Sections 8-10.
- It is understood that statistical non-significance is not an indicator of equivalence.

7.4 Subgroups

Differences in safety and/or efficacy by subgroups defined by the following classifiers may be explored as part of the final analysis:

- Ambulatory vs. non-ambulatory
- LVEF: $\geq$ 55% vs. < 55%
- Initiation of eteplirsen while on trial
- Baseline DSA MFI < 500 vs. 500-1000 and/or DSA quartiles
- Donor, stromal cell derived factor 1 (SDF1) level of lot received, master cell bank, and/or other identified measures of potential cell potency

In addition, differences in safety and/or efficacy based on exposure to various heart failure medications, such as mineralocorticoid receptor antagonist (MRA), may be explored.

7.5 Missing Data

- Listings will present data as reported.
- Missing or partially missing dates that are required for date-dependent definitions (e.g., treatment-emergent AEs, concomitant medications) will be assumed to be the most conservative date possible. For example, an AE with a completely missing start date will

be considered treatment-emergent; similarly, an AE that started the same month and year as IP administration but with missing start day will be considered treatment-emergent.

- Handling of missing endpoint data in summaries and analyses for each endpoint is described in Sections 8-10.

7.6 Study Period and Time Point Definitions

The following study periods and time points are defined:

Screening Period: the 30-day time period before IP infusion or the reference time point.

Baseline: for a given parameter for a given subject, the last observation before IP infusion or the reference time point.

Day 0: for a given subject, the day of planned IP infusion or the reference day.

(Nominal Visit) Analysis Time Point: analysis based on data collected at the *(nominal visit)* time point, where nominal visits are as shown below in Section 7.7.

End of Study (EOS), Subject Level: subject-level EOS is reached after completion of the Month 12 visit or discontinuation for any reason.

EOS, Study-Level: EOS is reached when all randomized subjects have either completed the Month 12 visit or have discontinued from the study for any reason.

Long-Term Follow-Up (LTFUP) Period, Subject-Level: the LTFUP period begins after completion of the Month 12 visit and continues until 4 more annual visits have been completed.

7.7 Visit Windows

Study visits will include Screening, Day 0, and nominal week or month indicated in the table below. Visit windows will be used in data listings, summaries and analyses and will be based on study day of the observation, defined as:

study day = date of observation – Day 0 date

Visit windows per protocol and to be used in listings, summaries and analyses are as follows:

Nominal Visit	Nominal Day	Min Day Per Protocol	Max Day Per Protocol	Min Day for Analyses	Max Day for Analyses
Week 2	14	11	17	1	29
Week 6	42	33	47	30	61
Month 3	90	83	97	62	153
Month 6	180	166	194	154	275
Month 12	360	330	390	276	427

where cell entries are study days as defined above. For example, per protocol the Month 3 visit will occur between 83 and 97 days post infusion (Day 0), but for purposes of listings, summaries

and analysis all observations dated between 62 and 153 days post infusion will be included in the Month 3 visit window.

Efficacy assessments that occur too late to be included in the Month 12 analysis window will be included in "last observation" analyses (see Section 10).

For ITT summaries and analyses, study day will be defined as:

study day = date of observation – randomization date - X

where X is the number of days between randomization and Day 0.

For example, for a subject who received IP 5 days after randomization and who had an assessment 65 days after randomization, the study day for that assessment would be 60 and the assessment would therefore fall into the Week 6 analysis window.

In addition, visit windows based on time of data collection will be defined for assessments done during the 24 hours post IP administration as follows:

Nominal Visit	Nominal Hour	Min Hour for Analyses	Max Hour for Analyses
8 Hours Post	8	4.01	12.00
16 Hours Post	16	12.01	20.00
24 Hours Post	24	20.01	28.00

If multiple valid, non-missing observations exist within a given window, the observation to be used will be:

1. the observation closest to the nominal visit day in question, or
2. the latest observation if the multiple observations are equidistant from the nominal visit day, or
3. the average (arithmetic or geometric, as appropriate) of the observations if the multiple observations have the same actual time point. In instances of multiple observations with the same time point from different laboratories, only observations from the central laboratory will be used.

8. STUDY POPULATION PARAMETERS

Listings will be done for the ITT population and summaries for the safety population. Some or all summaries may also be done for other analysis populations defined in Section 6. Study population parameters to be listed and summarized are described below.

8.1 Analysis Populations

The analysis populations defined in Section 6 will be described in terms of the identification of subjects in each population and the frequency distribution of each population.

8.2 Eligibility and Informed Consent

Eligibility and informed consent parameters will be listed and will include protocol version, date of informed consent, and inclusion and/or exclusion criteria that were not met. Satisfaction of inclusion/exclusion criteria will be summarized.

8.3 Baseline Characteristics

Demographic and other baseline characteristics will be listed and summarized and will include study site, age, race, ethnicity, Latin or Hispanic origin, DMD genetic analysis, and frequency of wheelchair use. Age will be computed in SAS as follows:

AGE = floor((intck('MONTH', bdt, rdt) - (day(rdt) < day(bdt))) / 12)

where bdt = birth date in SAS date format and rdt = randomization date in SAS date format.

Differences in baseline parameters by treatment group will be analyzed and p-values will be included in the summary table.

8.4 Medical History

General medical history and cardiac history will be listed and summarized separately. The general medical history summary will include frequency of subjects with each condition. For cardiac history, the number of subjects with each condition and other condition-specific details will be summarized. Differences in medical and cardiac history by treatment group will be analyzed and p-values (for frequencies only) will be included in the summary table.

8.5 Serology and Coagulation

Serology laboratory evaluations will include human immunodeficiency virus (HIV), hepatitis B surface antigen (HBsAg), and hepatitis C virus (HCV) and will be done at screening. Coagulation laboratory evaluations will be done pre-infusion (CAP-1002 subjects only). Serology and coagulation parameters will be listed and summarized.

8.6 IP Administration

Details of IP administration will be listed. Successful completion of IP administration, reason for non-completion, combination of coronary territories infused, total dosage, and final TIMI flow score per artery infused will be summarized.

8.7 Subject Study Progress

A listing of subject study progress will show dates of screening, informed consent, randomization, IP administration, study visits, and EOS. Number of subjects who completed each visit will be summarized.

8.8 Subject Disposition

A listing of subject disposition will include dates of randomization and IP administration (or attempt) or reference date, whether or not the subject completed the Month 12 visit, subject-level EOS date, reason for study discontinuation (if applicable), and whether or not the subject consented to annual LTFUP. Frequencies and percentages of subjects who discontinued and reasons for discontinuation as well as duration of follow-up will be summarized. Duration of follow-up will be calculated as:

duration = date of last known status – randomization date + 1

where date of last known status is the maximum date among AE start and end dates, concomitant medication start and stop dates, visit dates (including unscheduled visits), and EOS date.

The summary table will include a p-value for treatment group comparison of discontinuation for any reason and, if appropriate, for duration of follow-up based on a log rank test.

9. SAFETY ANALYSIS

Listings, summaries, and analyses of safety parameters will be done for the safety population. Some or all summaries may also be done for other analysis populations defined in Section 6. Safety parameters are described below.

9.1 Adjudicated Clinical Events

Clinical events, described in Section 2.3.1, will be adjudicated by an independent Clinical Events Committee (CEC) (see Section 12). Each event will be summarized as frequency and percentage of subjects who experienced the event. In addition, a composite event will be defined as new TIMI flow 0-2 or TMPG 0-2 (CAP-1002 subjects only), sudden death, or MACE during or following IP administration or reference time point. For the composite and its components, summaries will include exact 90% confidence intervals (CIs) for both treatment groups. For peri-procedural events other than TIMI flow 0-2 or TMPG 0-2, summaries will include a 90% CI for the difference in proportions between treatment groups, and the one-sided p-value from an exact binomial test of the difference between treatment groups. For all other clinical events, assessed over the length of the trial, event rates per 100 subject-years will be calculated and, if applicable, treatment groups will be compared using negative binomial regression with an offset for days of follow-up (log transformed). If the dispersion parameter is not significantly different from zero, Poisson regression will be used instead.

For the analysis of development of increased HLA antibodies to HLA antigens specific to the CAP-1002 donor, incidence of increased HLA antibody levels specific to the donor will be summarized and analyzed; for usual care subjects, a random donor will be selected from those that were matched to the subject during screening. Elevated levels of donor specific antibodies will also be summarized and analyzed by time point for all nominal time points at which samples were collected for DSA testing. Analyses will be performed using both 1000 and 5000 MFI as the threshold for defining increased HLA antibodies.

9.2 Adverse Events

AEs reported from screening through EOS will be coded according to MedDRA® (Medical Dictionary for Regulatory Activities) version 19.0. Each reported AE will be mapped to a Preferred Term (PT) and a System Organ Class (SOC). A subset of AEs (indicated below) will also be adjudicated by the independent CEC.

A treatment-emergent AE (TEAE) will be defined as an AE that began or worsened during or after the IP administration procedure or on or after the reference time point. AEs with insufficient date or time information to determine whether or not they were treatment-emergent will be considered treatment-emergent and the ambiguity regarding start time/date for these AEs will be footnoted in summary tables.

All TEAEs will be listed as reported. A separate listing will be done for TEAEs as adjudicated by the CEC. In addition, separate listings will be done for deaths, non-treatment-emergent AEs and serious AEs (SAEs), treatment-emergent SAEs (adjudicated), TEAEs within 24 hours of IP administration (adjudicated if judged to be related to IP or IP administration procedure), and TEAEs that resulted in study discontinuation (excluding deaths); these listings will be "as adjudicated," as applicable. Deaths will be listed by primary cause as adjudicated by the CEC.

Incidence and number of TEAEs will be summarized by SOC and PTs within SOCs, both overall and by relationship to IP, relationship to IP administration, and severity. Relationship status "possibly," "probably," or "definitely" will be considered related and will be adjudicated. Missing relationship will be considered related for subjects in the CAP-1002 group and missing severity will be considered severe; the lack of assigned relationships for these AEs will be footnoted in summary tables. Only the most related TEAE per subject for a given PT will be counted in summaries by relationship; similarly, only the most severe TEAE will be counted in summaries by severity. Separate summaries will be done for treatment-emergent SAEs, TEAEs within 24 hours of IP administration, treatment-emergent deaths, and TEAEs resulting in study discontinuation (excluding deaths). Each summary table will include a p-value for the comparison of incidence for each SOC and PT, as well as overall, between treatment groups, if applicable. Summary tables and analyses will be based on TEAEs as adjudicated by the CEC.

9.3 Concomitant Medications

Medication use from consent through EOS will be coded to generic terms using the World Health Organization Drug Dictionary (WHO-DD), version June 1, 2016. Listings will include IP administration date, WHO-DD drug class, WHO-DD preferred drug name, generic/trade drug name, start and stop dates, dose, route, frequency, indication, and associated AE and SAE number, if applicable. Frequencies and percentages of subjects reporting or receiving each medication will be summarized by WHO-DD drug class and preferred name within drug class. Any pre-infusion/reference date medications reported will be listed and summarized separately from concomitant medications. Cardiac and steroid medications will also be listed and summarized separately. Medications that were stopped no later than the day before IP administration or reference day will be considered "pre-infusion." All other medications will be considered "concomitant." Medications recorded with insufficient exposure dates to determine whether or not they were concomitant will be considered concomitant.

9.4 Safety Laboratory Evaluations

Specific laboratory evaluations to be performed are detailed in Appendix 2 of the protocol. Listings of safety laboratory evaluations will include study visit, date and time of collection, normal ranges, observed values with out-of-range values flagged, and changes from baseline. Separate series of listings will show out-of-range observations.

Observed values and changes from baseline will be summarized by study visit. A separate series of summaries will show incidence of out-of-range observations by study visit. Shift tables will summarize shifts from one out-of-range category at baseline to another out-of-range category at each subsequent study visit and will include p-values for treatment group differences.

Listings and summaries will be done separately for each of the following laboratory evaluations or groups of evaluations:

- Serum chemistry (basic metabolic and comprehensive hepatic panels)
- Hematology
- Urinalysis
- Glycosylated hemoglobin (HbA1c)
- Cardiac (troponin I, troponin T, CK-MB)
- Immunogenicity (HLA, DSA, enzyme-linked immunosorbent spot (ELISPOT))
- Exploratory biomarkers, if available

For DSA, the raw data will be provided by the core laboratory and a listing of HLA antibodies and specific alleles will be provided to the independent clinical immunologist to make the final determination of which are DSA caused by sensitization to the donor cells, and which are non-specific changes that are not due to donor-specific sensitization. Any summary tables or analyses of DSA will be based on DSA as adjudicated by the independent clinical immunologist.

The results of the ELISPOT assay for the tested samples will be reported as number of spots/400,000 cells/well. In addition, the results will be expressed as mean and standard deviation (SD) of the triplicate (or duplicate) wells for serum-free medium wells, fetal bovine serum (FBS)-containing medium wells, and antigen-stimulated wells. For phytohemagglutinin (PHA)-stimulated wells the result will be the spot number/400,000 cells from the single well. If the cell number would be insufficient and the testing will be performed in a single well for a given variant, then the result will be the spot number/400,000 cells from the single well. A positive or negative response to each antigen (cardiac cell lines) will be determined based on the results of each individual sample. A positive response will be defined as greater than Y + 2SD of Y number of spots after exposure to Antigen (X) and more than 10 spots, whereby:

Y: Average spot number in the FBS-medium control (cells and no antigen)

X: Average spot number to the given antigen (cells and antigen)

The antigen specific response = antigen positive response = X - (SD of X) – [Y + (2SD of Y)] and has to be greater than the numerical value 3. All negative values generated by the formula above will be reported as 0 spot values, as negative values are biologically irrelevant.

The results for the control sample will be reported as number of spots/400,000 cells/well. In addition, the results will be expressed as mean and SD of the triplicate wells for medium wells, antigen-stimulated wells and PHA wells.

Any clinical sample that will produce below 100 interferon-gamma spots in response to the mitogen (positive control) PHA will be flagged as non-functional and the ELISPOT results for that sample should be excluded from further analysis.

9.5 Vital Signs, Height, Weight, and BMI

Vital signs will include systolic and diastolic blood pressure, heart rate, respiratory rate, and body temperature. Listings of vital signs, height, weight, and BMI will include study visit, date and time of collection, observed values, and changes from baseline. Observed values and changes from baseline will be summarized by study visit. BMI will be calculated as:

$$BMI = \frac{weight\ (kg)}{(height\ (m))^2}$$

9.6 Physical Examination

General and cardiac physical examination findings will be listed and summarized separately. General physical examination findings will be summarized either as frequencies of normal/abnormal indicators at each visit or, if appropriate (i.e., if data are not too sparse), as shifts from baseline in normal/abnormal indicators for each body system. For cardiac physical examination findings, the number of subjects with each condition and other condition-specific details will be summarized; shifts from baseline in present/absent and normal/abnormal indicators will also be summarized, as will murmur grade.

9.7 12-Lead ECG and Continuous Cardiac Monitoring

Listings of 12-lead ECG parameters will include study visit, date and time of ECG, and observed values. Observed values and changes from baseline in ventricular rate and interval parameters (QRS, PR, QT, QTc) will be summarized by study visit. Overall interpretation of 12-lead ECG will also be summarized.

Listings of continuous cardiac monitoring parameters will include study visit, start and stop date/time, and observed values. Observed values and changes from baseline in QRS complexes, paced QRS complexes, ventricular ectopic beats, supraventricular ectopic beats, heart rates, and longest RR will be summarized by study visit. Presence of atrial fibrillation, including number of episodes and longest run, will also be summarized.

10. EXPLORATORY EFFICACY ANALYSIS

Listings of efficacy parameters will be done for the ITT population. Summaries and analyses will primarily be done for the mITT population; some or all summaries and/or analyses may also be done for other analysis populations defined in Section 6. In addition, “last observation” analyses will be done for certain parameters for which some subjects’ final assessments were done too late to be included in the Month 12 analysis window.

Unless otherwise noted, for the final analysis changes from baseline will be analyzed using general linear models with baseline values as covariates. Analyses of the effect of treatment group, time (baseline, Month 6, Month 12), and their interaction will be done using mixed effects linear regression, with subject as a random effect, time and treatment group as fixed effects, and baseline as a covariate. Study site may also be included as a random effect if there is evidence of correlation within study sites (per the interclass correlation coefficient from the unconditional model) and/or if doing so appreciably improves the model fit (e.g., per Akaike’s Information Criterion). Residuals will be evaluated for substantial departure from normality and independent and constant variance and appropriate remedies (e.g., data transformations, detecting and assessing the influence of outliers, alternative analytical approaches) will be attempted when necessary. An unstructured covariance will be the default covariance structure but other structures (e.g., compound symmetry) may be used to evaluate sensitivity to the choice of structure or, if necessary, to achieve convergence.

For the analysis of LV LGE rate of change since baseline compared to rate of change from historical MRI to baseline, rate of change $RC(t_i)$ for time point t_i, i = 1 to 3 (baseline, Month 6, Month 12, respectively), will be calculated as

$$RC(t_i) = (X(t_i) - R(t_i)) / D(t_i)$$

where $X(t_i)$ is observed LGE at t_i, $R(t_i)$ is observed LGE at the reference time point for t_i, and $D(t_i)$ is the number of days between t_i and the reference time point for t_i. The reference time point will be the date of historical MRI for i = 1 and baseline for i > 1. The mixed effects model to be used for the final analysis will be similar to that described above, with historical LGE included as a covariate. The LSMEANS procedure in PROC MIXED will be used to compare $RC(t_2)$ and $RC(t_3)$ to $RC(t_1)$ within each treatment group, and tests for interaction along with descriptive statistics will be used to evaluate differences by treatment group.

Assuming missing observations are "missing at random" (MAR), i.e., the fact that they are missing is unrelated to the missing variable but can be related to another variable on which data have been collected, the maximum likelihood (ML) approach is able to handle subjects with either Month 6 or Month 12 changes from baseline missing, but not both. Therefore, for final analyses based on the mITT population, missing data will be addressed using ML. Final analyses based on the ITT population may include subjects with both Month 6 and Month 12 changes from baseline missing; under these circumstances, multiple imputation will be used based on all observations and will use a fully conditional specification method with 20 burn-in iterations and the regression method of imputation. Variables in the imputer's model will be baseline observation (because baseline is used as a covariate in analyses), Month 6 change from baseline, Month 12 change from baseline, and treatment group. Because the MAR assumption is not testable, and because it seems possible that subjects with poorer outcome may be more likely to miss trial assessments, a sensitivity analysis under a "missing not at random" (MNAR) assumption may be done (for the final analysis only) for any efficacy endpoint for which all change from baseline measurements are missing for some subjects. For the MNAR model, multiple imputation will use the pattern-mixture model approach to address missing values; i.e., the imputation will be based on a pre-specified subset of subjects: for this MNAR analysis, only subjects randomized to usual care. Because very few missing observations are expected in this trial, 5 imputed data sets will be used for all analyses using multiple imputation.

For all analyses of all efficacy parameters, tests of treatment effect will be based on comparisons of least-squares (LS) means with no adjustment for multiple comparisons.

Efficacy parameters are described below.

10.1 MRI Parameters

Data for MRI parameters detailed in Section 2.3.2 will be delivered in a raw file provided by the MRI Core Lab. Observed values, absolute changes from baseline, and percent changes from baseline will be listed and summarized. Summary tables will include p-values for treatment group comparisons of changes from baseline.

Regional wall motion will be analyzed using average (over slices) end diastolic wall thickness, end systolic wall thickness, and wall thickening. Sixteen-segment data correspond to coronary region as follows:

- Left anterior descending artery = segments 1, 2, 7, 8, 13, and 14.
- Left circumflex artery = segments 5, 6, 11, 12, and 16.
- Right coronary artery = 3, 4, 9, 10, and 15.

Different coronary anatomy will be associated with specific segments on a case-by-case basis. Analysis parameters will be observations averaged over the infused segments. For example, if the infused segment is via the right coronary artery, wall thickening for that location will be the mean "average" wall thickening over segments 3, 4, 9, 10, and 15.

Regional wall motion will also be analyzed according to circumferential location as follows:

- Anterior = 1, 7, and 13
- Lateral = 5, 6, 11, 12 and 16
- Inferior = 4, 10, and 15
- Septal = 2, 3, 8, 9, and 14

Of note, segments 2 and 3 will be excluded for all wall thickness analyses.

Scar size, non-viable tissue, and circumferential strain will be analyzed both overall as well as by individual segments and the following groups of segments:

- By coronary artery territory as follows:
    - Left anterior descending artery = segments 1, 2, 7, 8, 13, and 14
    - Left circumflex artery = segments 5, 6, 11, 12, and 16
    - Right coronary artery = 3, 4, 9, 10, and 15

- By circumferential location as follows:
    - Anterior = 1, 7, and 13
    - Lateral = 5, 6, 11, 12 and 16
    - Inferior = 4, 10, and 15
    - Septal = 2, 3, 8, 9, and 14

Listings of MRI parameters will include observed values, changes from baseline, and percent changes from baseline. A summary table will include p-values for treatment group comparisons of changes from baseline.

MRI overreaders will be blinded to treatment assignment but not to temporal order of the images; e.g., readers will have access to and will use baseline and Month 6 images when reading Month 12 images (informed reading).

10.2 Mobility Parameters

10.2.1 PUL Scale

The PUL Scale consists of an entry item to define the starting functional level and 21 items subdivided into shoulder level (4 items, maximum score = 16), middle level (9 items, maximum score = 34), and distal level (8 items, maximum score = 24) dimensions. The three dimensions will be summed to derive an overall score (maximum = 74) as well as an overall score that excludes the shoulder dimensions (maximum = 58). The minimum score for all three dimensions is 0. Increasing scores over time indicate improvement. Observed values and absolute changes from baseline, overall and for each dimension separately, will be listed and summarized. A summary table will include p-values for treatment group comparisons of changes from baseline.

10.2.2 Spirometry

Spirometry parameters include peak expiratory flow (PEF), forced expiratory volume in 1 second (FEV_1), forced vital capacity (FVC), FEV_1/FVC x 100, forced expiratory flow at 25-75% of FVC ($FEF_{25-75\%}$), and forced expiratory time (FET). Observed values, percent of predicted, and absolute and percent changes from baseline will be listed and summarized. A summary table will include p-values for treatment group comparisons of changes from baseline. Extreme outliers, defined as any observation outside the range [q1 – 3(q3 – q1), q3 + 3(q3 – q1)] where q1 and q3 are the 25th and 75th percentiles, respectively, over all observations for a given parameter (regardless of time point) will be excluded from summaries and analyses.[6]

10.2.3 6MWT

For distance walked in the 6MWT of the subset of ambulatory subjects, observed values, absolute changes from baseline, and percent changes from baseline will be listed and summarized. A summary table will include p-values for treatment group comparisons of changes from baseline. Because of potential differences in 6MWT administration procedures across study sites, "site" will be carefully considered as a potential source of excess variation and will be included in the statistical model as a random effect if warranted.

10.3 QoL

The following QoL measurement instruments, although routinely used for DMD trials, have not been validated for young adults, and this trial will enroll subjects > 18 years old.

10.3.1 PedsQL – DMD Module

The PedsQL-DMD Module consists of 18 items and results in scores for each of 4 scales (Daily Activities, Treatment Barriers, Worry, Communication) and a total summary score. Separate inventories are typically used for respondents 13-18 years old and for respondents 8-12 years old, as well as for parent responders for each age category; however, in this trial, only the inventories for 12-18 year-olds will be used, despite the lower age limit for trial inclusion being 12 years. While responses to all 18 items will be listed, only these 4 scales and the total score will be summarized. Summary tables and listings will include observed values and changes from baseline; tables will also include p-values for treatment group comparisons of change from baseline.

The PedsQL is scored as follows:

1) Transform 0-4 scale items to 0-100 as follows: 0=100, 1=75, 2=50, 3=25, 4=0.

2) A score for each scale is calculated as the mean of the non-missing items that comprise that scale.

3) The Total summary score is the mean of all non-missing items.

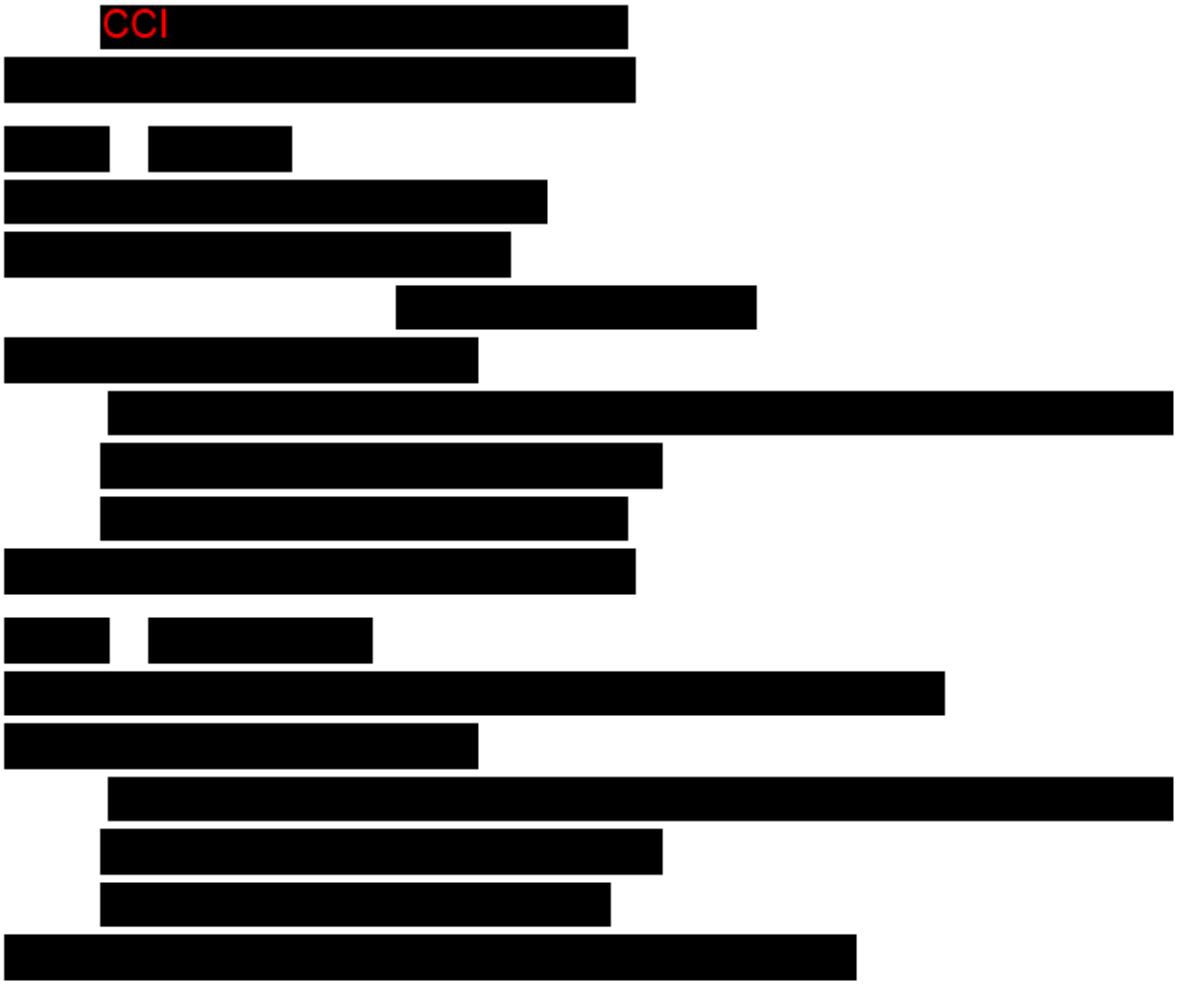
Decreasing scores over time indicate improvement.

10.3.2 Pediatric Outcomes Data Collection Instrument (PODCI)

The PODCI consists of 83 items and results in both standardized and normative scores for each of 6 scales. Decreasing scores over time indicate improvement. Separate inventories are used for subjects and for parent responders. While responses to all 83 items will be listed, only the 6 scales will be summarized. Summary tables and listings will include observed values and changes from baseline; tables will also include p-values for treatment group comparisons of change from baseline.

CCI

CCI



11. OTHER DATA COLLECTED

11.1 Missed Visits and Assessments

A listing of missed visits and assessments will show visit and/or assessment missed.

11.2 Protocol Violations/Deviations

Protocol excursions will be classified as either violations or deviations. Per ICH E3 (Structure and Content of Clinical Study Reports),[2] violations will be defined as:

- Enrolling into the trial without meeting all inclusion/exclusion criteria and without obtaining a waiver for any deviations from the protocol-defined entry criteria;
- Continuing in the trial after developing a withdrawal criterion (see Protocol Section 7.10);
- Receiving an incorrect dose or incorrect treatment; or
- Taking a prohibited concomitant medication (see Protocol Section 5.5).

Subjects with protocol violations will be excluded from the per protocol population. All other protocol discrepancies will be considered deviations and will be categorized for purposes of

summarization. Some protocol deviations may prohibit subjects from being in the per protocol population; this will be determined on a case-by-case basis before database lock.

In addition to the listings of inclusion/exclusion criteria detailed in Section 8.2 and missed visits and assessments detailed in Section 11.1, a separate listing will show all other protocol violations and will include protocol version, the category of the violation (to be determined), and an indicator for per protocol exclusion. Frequency and percentage of subjects in each violation category and excluded from the per protocol population will be summarized.

12. CLINICAL EVENTS COMMITTEE

In order to apply some level of consistency and standardization, the following will be adjudicated by a CEC:

- Clinical event endpoints
- AEs occurring within 24 hours of IP administration or reference time point (peri-procedural AEs)
- AEs judged by the investigator as possibly, probably or definitely related to the IP or IP administration procedure (related AEs)
- Treatment-emergent SAEs

The CEC will follow consensus definitions of cardiovascular endpoint events.[7] In the case where the protocol explicitly provides an endpoint definition, the CEC will adjudicate the clinical event according to the protocol definition and then, separately, according to the consensus definition. In the case where the protocol provides only a partial definition (e.g., "emergency room treatment for heart failure") or is silent on the definition of the endpoint, the consensus definition, if it exists, will be used.

For safety endpoints, a hierarchy will be applied for a clinical event that could be adjudicated in multiple categories so that a clinical event is counted only once. The hierarchy, from highest severity to lowest, will be death > heart failure hospitalization > cardiovascular-related hospitalization.

For any AE submitted to the CEC, all of the above characteristics will be adjudicated. In addition, the CEC can combine AEs reported separately into a single AE, can change the event description (i.e., the term used to report the AE), and can change the status of the reported event to a non-AE.

Any adjudicated event not otherwise named in the consensus definitions, as well as changed event descriptions, will be MedDRA-coded.

13. SEQUENCE OF PLANNED ANALYSES

13.1 Interim Safety Reviews

The DSMB will conduct an interim safety review after all subjects in Group 1 have completed at least 72 hours of observation (or withdrawn) and will make a recommendation on proceeding to Group 2 enrollment. Thereafter, the DSMB will conduct interim safety reviews at least every 6 months. For each DSMB meeting, the clinical study database will be reviewed, all data queries will be submitted to sites and resolved if possible, and a cut of the database will be taken on a specified date and used to produce TFLs for the DSMB.

13.2 Administrative Interim Analyses

13.2.1 Pre-Month 6

An administrative interim efficacy analysis will be performed when Month 6 MRI assessments are available for at least 14 subjects. Results from the interim efficacy analysis will be used for business planning activities to assure availability of therapeutic product and to plan subsequent clinical trials and will have no effect on the design or conduct of the trial. As such, there will be no statistical penalty applied to the final efficacy analysis as a result of the interim efficacy analysis. Personnel with access to unblinded data and analysis results will be detailed in an unblinding memorandum to be filed in the Trial Master File and to be submitted to regulatory agencies. Unblinded interim data and analysis results will be kept confidential from other company personnel involved with the trial conduct and from investigators, patients, and their families.

13.2.2 Month 6

An administrative interim efficacy analysis will be performed when all subjects in the mITT population have completed the Month 6 visit or have discontinued from the study. Results from the interim efficacy analysis will be used for business planning activities to assure availability of therapeutic product and to plan subsequent clinical trials and will have no effect on the design or conduct of the trial. As such, there will be no statistical penalty applied to the final efficacy analysis as a result of the interim efficacy analysis. A safety review similar to those done for the DSMB will also be done at this time. Top line results of the Month 6 administrative interim analysis will be reported publically. Clinical site trial personnel engaged in trial conduct and data collection will remain blinded to the complete interim data and analysis results, including patient level data. Imaging Core Lab personnel will remain blinded to treatment assignment and to all non-imaging patient level data until the final 12 month analyses.

13.3 Final Analysis

The final analysis will occur when all subjects have reached EOS (completed the Month 12 visit or discontinued), all clinical data have been entered into the data capture system, AE and concomitant medication data have been coded, quality control checks have been completed, all data queries have been resolved, protocol violations and the per protocol population have been identified, and the database has been locked.

14. DSMB

The DSMB will be appointed by the sponsor and will consist of physicians and at least one biostatistician who have no formal involvement or conflict of interest with the subjects, the sponsor, the investigators, or the clinical sites. The DSMB will communicate their findings directly to the sponsor.

Data on the following, in the form of TFLs and/or narratives, will be provided to the DSMB for review:

- Subject disposition
- Demographic and other baseline characteristics
- IP administration details
- Clinical event endpoints
- Treatment-emergent AEs and SAEs
- Safety laboratory evaluations
- Concomitant cardiac and steroid medications
- Continuous cardiac monitoring

In addition, the DSMB will be provided with TFLs from the Month 6 administrative interim efficacy analysis.

15. DEVIATIONS FROM STATISTICAL METHODS IN THE PROTOCOL

Section 9 of the protocol defines the mITT population differently than the SAP, as follows:

Protocol	Deviation
Modified ITT (mITT) Population: Subjects in the CAP-1002 treatment group who received the IP, and all subjects in the usual care treatment group who remain on study as of 9:00 am (subject's time zone) on Day 0.	Modified ITT (mITT) Population for Efficacy Parameter X: Subjects in the safety population who have at least one post-baseline observation for Parameter X.

REFERENCES

1. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Statistical Principles for Clinical Trials (E9), September 1998.

2. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Structure and Content of Clinical Study Reports (E3), November 1995.

3. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, Good Clinical Practice (E6), April 1996.

4. International Conference on Harmonisation of Technical Requirements for Registration of Pharmaceuticals for Human Use, ICH Harmonised Tripartite Guideline, General Considerations for Clinical Trials (E8), July 1997.

5. Antognini & Zagoraiou, Balance and randomness in sequential clinical trials: the dominant biased coin design, Pharm Stat 2014 (13), pp 119–127.

6. Tukey JW (1977). *Exploratory Data Analysis*. Addison-Wesley Publishing Company.

7. Hicks KA, Tcheng, JE, Bozkurt, B, et al. 2014 ACC/AHA key data elements and definitions for cardiovascular endpoint events in clinical trials: a report of the American College of Cardiology/American Heart Association Task Force on Clinical Data Standards (writing committee to develop cardiovascular endpoints data standards). J Am Coll Cardiol 2015;66:403-69.

APPENDIX A: SCHEDULE OF EVENTS

Procedure / Event	**Screening**	**Infusion**		**Week 2**	**Week 6**	**Month 3**	**Month 6**	**Month 12**	**Early Termination[1]**
Study Day	Day -30 to -1	Day 0		Day 14 (±3)	Day 40 (±7)	Day 90 (±7)	Day 180 (±14)	Day 360 (±30)	As Needed
		PRE	*POST*						
Informed Consent	X								
Eligibility Assessment	X	X							
Demographics	X								
Medical History	X	X							
Cardiac History	X	X							
Concomitant Medications	X	X	X	X	X	X	X	X	X
Vital Signs	X	X	X	X	X	X	X	X	X
Weight	X						X	X	X
12-Lead ECG	X	X	X	X	X	X	X	X	X
Limited Physical Examination	X							X	X
Cardiac Physical Examination	X	X	X	X	X	X	X	X	X
Cardiac MRI	X						X	X	X
24-Hour Ambulatory ECG via Holter Monitor or ZIO® Patch	X		X		X		X	X	X
Clinical Laboratory Tests (includes Chemistry, Hematology, Urinalysis)	X	X	X	X	X	X	X	X	X
Serology[2]	X								
Osteopontin	X			X	X	X	X	X	X
ST2	X			X	X	X	X	X	X
IL-10	X			X	X	X	X	X	X
Galectin-3	X			X	X	X	X	X	X
Exploratory Biomarkers	X			X	X	X	X	X	X
HLA	X								

Procedure / Event	**Screening**	**Infusion**		**Week 2**	**Week 6**	**Month 3**	**Month 6**	**Month 12**	**Early Termination[1]**
Study Day	Day -30 to -1	Day 0		Day 14 (±3)	Day 40 (±7)	Day 90 (±7)	Day 180 (±14)	Day 360 (±30)	As Needed
		PRE	*POST*						
DSA	X			X	X	X	X	X	X
ELISpot		X			X				
PUL scale	X				X	X	X	X	X
6MWT	X				X	X	X	X	X
Pediatric QL Inventory	X				X	X	X	X	X
PODCI	X				X	X	X	X	X
Spirometry	X				X	X	X	X	X
Coagulation		X							
Serum Troponin & CK-MB		X	X	X			X	X	X
Intracoronary Infusion		X							
Adverse Event Assessment	X	X	X	X	X	X	X	X	X

[1] Early Termination Visit procedures to be completed at time of withdrawal, should subject be withdrawn before Month 12 Visit. A Cardiac MRI will be conducted provided the subject's most recent study-related Cardiac MRI was conducted at least three months (i.e., 12 weeks) prior to the Early Termination Visit.

[2] Serology includes HIV and hepatitis testing

APPENDIX B: TABLES OF CONTENTS FOR TABLES, FIGURES, AND LISTINGS

TABLES

STUDY POPULATION

14.1.1	Number of Subjects by Study Visit
14.1.2	Subject Disposition
14.1.3.1	Inclusion/Exclusion Criteria Not Met
14.1.3.2	Protocol Violations
14.1.4	Analysis Populations
14.1.5	Demographics and Baseline Characteristics
14.1.6.1	General Medical History
14.1.6.2	Cardiac Medical History
14.1.7	Screening Labs
14.1.8	Investigational Product Administration

EFFICACY

14.2.1	MRI
14.2.2	PUL
14.2.3	6MWT
14.2.4	Spirometry
14.2.5.1	PedsQL, Subject
14.2.5.2	PedsQL, Parent
14.2.6.1	PODCI, Subject
14.2.6.2	PODCI, Parent

SAFETY

14.3.1.1.1	Composite Clinical Safety Endpoint
14.3.1.1.2	Other Clinical Safety Endpoints
14.3.1.2	Summary of Treatment-Emergent Adverse Events
14.3.1.3	Treatment-Emergent Adverse Events
14.3.1.4	Treatment-Emergent Adverse Events Within 24 Hours of IP Administration
14.3.1.5	Treatment-Emergent Adverse Events in Subjects with Peri-Procedural Troponin Elevations
14.3.1.6	Treatment Emergent AEs Resulting in Study Discontinuation
14.3.1.7	Treatment Emergent SAEs
14.3.1.8	Treatment-Emergent SAEs in Subjects with Peri-Procedural Troponin Elevations
14.3.1.9	Treatment-Emergent Deaths
14.3.1.10	Treatment-Emergent Adverse Events -- Preferred Terms in Order of Descending Incidence
14.3.5.1.1	Serum Chemistry
14.3.5.1.2	Serum Chemistry Out of Range
14.3.5.1.3	Serum Chemistry Shifts From Baseline
14.3.5.2.1	Renal Functioin
14.3.5.2.2	Renal Function Out of Range
14.3.5.2.3	Renal Function Shifts From Baseline
14.3.5.3.1	Hepatic Function
14.3.5.3.2	Hepatic Function Out of Range
14.3.5.3.3	Hepatic Function Shifts From Baseline
14.3.5.4.1	Hematology
14.3.5.4.2	Hematology Out of Range
14.3.5.4.3	Hematology Shifts From Baseline
14.3.5.5.1	Cardiac Biomarkers
14.3.5.5.2	Cardiac Biomarkers Out of Range
14.3.5.5.3	Cardiac Biomarkers Shifts From Baseline
14.3.5.6.1.1	Urinalysis (continuous)

14.3.5.6.1.2 Urinalysis (categorical)
14.3.5.6.2 Urinalysis Out of Range
14.3.5.6.3 Urinalysis Shifts From Baseline
14.3.5.7.1 Exploratory Biomarkers
14.3.5.7.2 Exploratory Biomarkers Out of Range
14.3.5.7.3 Exploratory Biomarkers Shifts From Baseline
14.3.5.8 DSA
14.3.5.9 ELISpot
14.3.6.1.1 Concomitant Medications
14.3.6.1.2 Concomitant Cardiac and Steroid Medications
14.3.6.2 Vital Signs
14.3.6.3 Weight, Height, Body Mass Index
14.3.6.4.1 General Physical Examination
14.3.6.4.2 Cardiac Physical Examination
14.3.6.5.1 12-Lead Electrocardiogram
14.3.6.5.2.1 Continuous Cardiac Monitoring (contiuous)
14.3.6.5.2.1 Continuous Cardiac Monitoring (categorical)

LISTINGS

STUDY POPULATION
16.2.1.1 Critical Dates and Scheduled Visits
16.2.1.2 Subject Study Visits
16.2.1.3 Subject Disposition
16.2.2.1 Informed Consent
16.2.2.2 Eligibility & Randomization
16.2.2.3 Protocol Violations
16.2.2.4 Missed Visits and Assessments
16.2.3 Analysis Populations
16.2.4.1 Demographics
16.2.4.2.1 General Medical History
16.2.4.2.2 Cardiac Medical History
16.2.4.3.1 Pre-Treatment AEs
16.2.4.3.2 Pre-Treatment SAEs
16.2.4.4.1 Pre-Treatment General Medications
16.2.4.4.2 Pre-Treatment Cardiac and Steroid Medications
16.2.4.5 Screening Labs
16.2.5 Investigational Product Administration

EFFICACY
16.2.6.1 MRI Parameters
16.2.6.2 PUL Scale
16.2.6.3 6MWT
16.2.6.4 Spirometry
16.2.6.5.1 PedsQL - Subject
16.2.6.5.2 PedsQL - Parent
16.2.6.6.1 PODCI - Subject
16.2.6.6.2 PODCI - Parent

SAFETY
16.2.7.1.1 Composite Clinical Safety Endpoint
16.2.7.1.2 Other Clinical Safety Endpoints
16.2.7.2.1 Treatment Emergent AEs as Reported
16.2.7.2.2 Treatment Emergent AEs as Adjudicated
14.3.2.1 Treatment Emergent SAEs
14.3.2.2 Treatment Emergent AEs Resulting in Study Discontinuation
14.3.2.3 Treatment-Emergent AEs in Subjects with Peri-Procedural Troponin Elevations
14.3.2.4 Treatment-Emergent AEs Resulting in Death

14.3.2.5 Treatment Emergent AEs Within 24 Hours
14.3.2.6 Cause of Death
16.2.8.1 Serum Chemistry
14.3.4.1 Serum Chemistry Out of Range
16.2.8.2 Renal Function
14.3.4.2 Renal Function Out of Range
16.2.8.3 Hepatic Function
14.3.4.3 Hepatic Function Out of Range
16.2.8.4 Hematology
14.3.4.4 Hematology Out of Range
16.2.8.5 Cardiac Biomarkers
14.3.4.5 Cardiac Biomarkers Out of Range
16.2.8.6 Urinalysis
14.3.4.6 Urinalysis Out of Range
16.2.8.7 Exploratory Biomarkers
14.3.4.7 Exploratory Biomarkers Out of Range
16.2.8.8 DSA
16.2.8.9 ELISpot
16.2.9.1.1 Concomitant Medications
16.2.9.1.2 Concomitant Cardiac and Steroid Medications
16.2.9.2 Vital Signs
16.2.9.3 Weight, Height, Body Mass Index
16.2.9.4.1 General Physical Examination
16.2.9.4.2 Cardiac Physical Examination
16.2.9.5.1 12-Lead Electrocardiogram
16.2.9.5.2 Continuous Cardiac Monitoring

FIGURES

EFFICACY
14.2.1.X MRI: Parameter X
14.2.2 6MWT
14.2.3.X Spirometry: Parameter X
14.2.4.X PUL: Parameter X
14.2.5.X.1 PEDS, Subject: Parameter X
14.2.5.X.2 PEDS, Parent: Parameter X

SAFETY
14.3.5.1.X Serum Chemistry Box Plots, Parameter X
14.3.5.2.X Renal Box Plots, Parameter X
14.3.5.3.X Hepatic Box Plots, Parameter X
14.3.5.4.X CBC Box Plots, Parameter X
14.3.5.5.1.1.X Cardiac Biomarkers Box Plots, Parameter X
14.3.5.5.1.2.X Cardiac Biomarker Box Plots, Parameter X -- Change from BL, non Post Infusion visits
14.3.5.5.2.X Cardiac Biomarker Spaghetti Plot, Parameter X -- Post Infusion, CAP-1002 only